REMARKS

Applicant respectfully requests reconsideration of the present application in view of the reasons that follow.

Claims 1, 11, 24, 124-159, 161-166, 168-169 are now pending and under examination in this application. The present status of all claims in the application is provided in the Listing of Claims, beginning on page 2 of this communication.

Rejection of claims under 35 USC § 103

Claims 1, 11, 129-139, 141-147, 156, and 165

The rejection of claims 1, 11, 129-139, 141-147, 156, and 165 under 35 USC § 103(a) as allegedly being obvious over Scherzinger et al. (European Journal of Biochemistry (1977) 72: 543-558) in view of Sorge et al. (US 5,556,772) and further in view of Tabor et al. (Journal of Biological Chemistry (1989), 264(11): 6447-6458) is respectfully traversed.

In order to establish a prima facie case of obviousness, the Examiner must demonstrate that the prior art (i) teaches or suggests every claim limitation, (ii) provides a motivation to combine (or modify) the teachings of the selected references, and (iii) provides a reasonable expectation of success. In *re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991); MPEP § 2143. Rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness. KSR Int'l Co. v. Teleflex Inc., 127 S.Ct. 1727, 1741 (2007) (quoting In re Kahn, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006)). Thus, in order to establish a *prima facie* case of obviousness, it is necessary for the Examiner to identify the reasons why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed. The proper analysis when determining obviousness includes consideration of the scope and content of the prior art; the level of ordinary skill in the prior art; the differences between the claimed invention and the prior art; and objective evidence of nonobviousness.

The instant claims are based, at least in part on the inventors' surprising and unexpected discovery that incubating template DNA molecule that does not have a terminal protein covalently bound to either 5' end with a reaction mixture including a DNA polymerase and at least one accessory protein at a constant temperature without exogenously-added oligonucleotide primers results in an amount of amplified product that is at least 10-fold greater than the amount of template DNA put into the mixture.

Specifically, instant claims 1, 129-139, 141-147, 156 distinguish over the art by requiring methods of amplifying a template DNA molecule that involve incubating the template DNA molecule with a reaction mixture comprising a DNA polymerase at a constant temperature to produce amplified product, wherein production of amplified product does not require exogenously-added oligonucleotide primers, and wherein the method is performed under conditions such that the amount of amplified product is at least 10-fold greater than the amount of template DNA put into the mixture.

As acknowledged by the Examiner, Scherzinger does not teach methods wherein the yield of the amplified product is at least 10-fold. Additionally, Scherzinger does not teach that the DNA polymerase comprises a mixture of T7 DNA polymerase with a normal level of 3' to 5' exonuclease activity and a T7 DNA polymerase with a reduced level of 3' to 5' exonuclease activity. As discussed in the previous response to Office Action mailed 12/11/2007, Scherzinger et al. merely discloses the role of T7 DNA-priming protein in DNA replication by T7 DNA polymerase (See for example, Scherzinger at P. 544, left column, lines 5-10).

The Examiner's reliance on Sorge et al. is unable to remedy the acknowledged deficiencies of Scherzinger et al. The Examiner alleges that it would be obvious to arrive at the instant invention by combining the DNA polymerase composition taught by Sorge et al. with the reaction mixture of Scherzinger et al. Applicant respectfully submits that the rejection fails because the cited references provide no teaching or suggestion that would motivate one of ordinary skill to combine the references to arrive at the instantly claimed method of amplification (which does not require exogenously added primers), nor is there any teaching that would

provide a reasonable expectation of success of achieving 10-fold amplification of target DNA in a reaction mixture including a DNA polymerase and at least one accessory protein at a constant temperature.

Contrary to the present invention, the Sorge's method of DNA amplification requires exogenously added oligonucleotide primers. This requirement of the Sorge's method is clearly stated in the Summary of the Invention:

> Other reagents **required** for polynucleotide synthesis include nucleotide triphosphates (dNTPs), **polynucleotide primers**, a synthesis template and the like.

Column 2, lines 39-41 (emphasis added). Moreover, each of the examples disclosed in the Sorge patent utilize exogenously added oligonucleotide primers; there is no teaching or suggestion that the methods could be used without such primers. Accordingly, Applicant respectfully submits that the Sorge reference would not motivate one of ordinary skill to use the DNA polymerases of the reference in a method that does not require exogenously added oligonucleotide primers (as contemplated by the instant claims). Furthermore, because the methods of Sorge et al. depend on exogenously added oligonucleotide primers for amplification, there would be no reasonable expectation of successfully practicing the claimed method which does not require such primers. Additionally, contrary to the Examiner's assertion, there was no reasonable expectation of success that the combination of Scherzinger et al. and Sorge et al. would achieve at least 10-fold amplification of the template DNA over the starting amount.

Applicants respectfully disagrees with the Examiner's effort to support the rejection by asserting that one of ordinary skill would allegedly be motivated to modify and combine the methods of Scherzinger and Sorge (as explained above, there is no such motivation), and that using "routine optimization" one could allegedly improve the yield of DNA amplifications and allegedly anticipate successfully meeting the claimed levels of amplification. Since Scherzinger discloses at best a 4-fold amplification of DNA (See, Scherzinger et al. at p.549, col. 2), modifying Scherzinger's method such as to arrive at the instant claims would require more than **doubling** the degree of DNA amplification achieved by the Scherzinger method. Contrary to the

Examiner's assertion, one of ordinary skill would not expect mere routine optimization to produce result in such a large increase in amplified DNA.

The Examiner's further reliance on Tabor et al. is unable to remedy the deficiencies of Scherzinger et al. and Sorge et al. Tabor et al. fails to disclose methods of amplifying a template DNA molecule by at least 10-fold in a reaction mixture comprising a DNA polymerase at a constant temperature to produce amplified product, wherein production of amplified product does not require exogenously-added oligonucleotide primers. Tabor et al. merely discloses wild-type and variant forms of T7 DNA polymerase.

Applicant provides herewith a Declaration under 37 C.F.R. § 1.132 by one of the inventors of this application, Dr. Stanley Tabor ("Tabor Declaration"), indicating that there was no suggestion in the art as to how one would modify Scherzinger's method to achieve greater than 10-fold amplification. (See, Tabor Declaration, at ¶¶ 5-9). Thus, it is only by improperly relying on the data first presented in the instant application that one of ordinary skill could have any reasonable expectation of successfully achieving the claimed methods. Accordingly, even if there were motivation to combine the references in the exact manner necessary to arrive at the instantly claimed method (there is not), the rejection still fails for a lack of reasonable expectation of success.

Thus, the combination of Scherzinger et al., Sorge et al., and Tabor et al. fails to establish a *prima facie* case of obviousness at least because there was no motivation to combine or modify the cited references in a manner such that one would arrive at the claimed invention. Even if there was such motivation (although there is none), the combination of references still fails to provide any reasonable expectation of success of achieving the claimed method.

With regard to claim 11 (directed to a method of amplifying a template DNA molecule comprising incubating said template DNA molecule with an *in vitro* reaction mixture comprising a DNA polymerase, a helicase, and a primase at a constant temperature to produce amplified product, wherein said method is performed under conditions such that the amount of amplified product is at least 10-fold greater than the amount of template DNA put into the mixture) the

Examiner points to nothing in the references that would disclose, teach or suggest a method contemplated in claim 11. Even if the references could be combined to meet each of the claim elements, the Examiner does not identify any disclosure in the art which provides any valid motivation to make the combinations or modifications required to arrive at the instantly claimed method. Moreover, the Examiner does not identify any disclosure in the art which provides a reasonable expectation of success of achieving at least 10-fold amplification of input target DNA (See, Tabor Declaration at ¶¶ 5-9).

Accordingly, this rejection should be withdrawn.

Claims 24 and 160

The rejection of claims 24 and 160 under 35 USC § 103(a) as allegedly being obvious over Scherzinger et al. in view of Sorge et al. and further in view of Bernstein et al. (Proceedings of National Academy of Sciences (1988), 85: 396-400) is respectfully traversed.

Instant claim 24 is directed to an isothermal method of amplifying a template DNA molecule comprising incubating the template DNA molecule in an *in vitro* reaction mixture comprising a wild-type T7 DNA polymerase and a T7 DNA polymerase modified to have reduced 3' to 5' exonuclease activity, a 63-kDa form of a gene 4 protein from bacteriophage T7 and a single-stranded binding protein from *Escherichia coli* to produce amplified product, wherein production of amplified product does not require exogenously-added oligonucleotide primers and the amount of amplified product is at least 10-fold greater than the amount of template DNA put into the mixture.

As discussed above, the combination of Scherzinger et al. and Sorge et al. fail to disclose, teach or suggest the claimed method of isothermally amplifying a template DNA without adding exogenous primers by incubating the template DNA without terminal protein covalently attached to either 5'-end, in a reaction mixture comprising DNA polymerase and at least one accessory protein to produce an amplified product such that the amplified product is at least 10-fold greater than the amount of template DNA put into the mixture.

The Examiner's reliance on Bernstein et al. is unable to remedy the deficiencies of Scherzinger et al. and Sorge et al. Bernstein et al does not disclose any method of amplifying template DNA by incubating the template DNA in a reaction mixture to produce an amplified product such that the amplified product is at least 10-fold greater than the amount of template DNA put into the mixture. Thus, Bernstein fails to cure the deficiencies of the other references.

Accordingly Applicant requests that this rejection be withdrawn.

Claims 124-128, 157-159, 166, and 168

The rejection of claims 124-128, 157-159, 166, and 168 under 35 USC § 103(a) as allegedly being obvious over Scherzinger et al. in view of Sorge et al. and further in view of Tabor et al. and Walker et al. (Nucleic Acids Research (1992), 20(7): 1691-1696 is respectfully traversed.

In this Office Action, the Examiner added claim 124 to the previous rejection and merely restated the rejection without providing any further insight into any motivation to combine or modify the references in the precise manner that would be required to arrive at the present claims. Specifically, the Examiner does not identify any disclosure in the art which provides any valid motivation to make the combinations or modifications required to amplify a template DNA molecule by at least 10-fold in a reaction mixture comprising a DNA polymerase at a constant temperature to produce amplified product, wherein production of amplified product does not require exogenously-added oligonucleotide primers. Furthermore, the Examiner does not identify any disclosure in the art which provides a reasonable expectation of success of achieving at least 10-fold amplification of input target DNA, let alone 100-10,000,000-fold amplification or exponential amplification.

The combination of Scherzinger et al., Sorge et al., or Tabor et al. alone and in combination fail to disclose, teach or suggest any method of isothermally amplifying a template DNA in a reaction mixture comprising DNA polymerase and at least one accessory protein such

that the amount of amplification product is at least 100-fold greater than the amount of template DNA put into the reaction mixture as required by the instant claims.

As acknowledged by the Examiner Scherzinger et al. does not teach 100-10,000,000-fold amplification or that the amplification is exponential. The Examiner's reliance on Walker et al. is unable to remedy the deficiencies of the primary reference.

Walker et al. fails to cure the deficiencies of Scherzinger et al., Sorge et al, and Tabor et al. In particular, the methods disclosed in Walker, like those of Sorge, require the addition of exogenously added primers. *See* Walker at page 1691, right column, lines 15-16. As described above, one of ordinary skill in the art would have no motivation to combine primer-based amplifications such as those disclosed in Walker with the primer-free DNA replication reactions disclosed in Scherzinger.

Moreover, even if there was motivation to combine and modify the methods of the cited art, there would be no reasonable expectation that any such method could possibly yield the amounts of amplified product required by the instant claims without the use of exogenously added primers. In this regard, as explained above, the art does not provide a reasonable expectation of achieving the 10-fold amplification required by the other claims. Instant claims 124-128, 157-159, 166, and 168 require a 100-10,000,000-fold amplification or that the amplification is exponential. Thus, modifying the Scherzinger method such as to arrive at the instant claims would require amplifying more than **25-times** the DNA amplified by the Scherzinger method (achieving the levels required by claim 127 would require improving the Scherzinger method such as to achieve more than **2.5-million times** the amount of DNA) (See Tabor Declaration at ¶¶ 5-9). Accordingly, without the benefit of the data presented in the instant application, there is absolutely no expectation that the Scherzinger method could be "optimized" such as to result in the amplification levels required by the instant claims.

Accordingly, this rejection should be withdrawn.

Claim 140

The rejection of claim 140 under 35 USC § 103(a) as allegedly being obvious over Scherzinger et al. in view of Sorge et al. and further in view of Tabor et al., and Bernstein et al. (Proceedings of National Academy of Sciences (1988), 85: 396-400) is respectfully traversed.

The Examiner has merely restated the previous rejection. As discussed previously, none of the cited prior art alone or in combination disclose a method of amplifying template DNA isothermally such that the amplified product is at least 10-fold greater than the input amount as required by instant claim 140. Furthermore, there is neither any motivation to combine the cited prior art methods nor any reasonable expectation that the claimed method could be successfully achieved.

The rejection should be withdrawn.

Claims 148 and 149

The rejection of claims 148 and 149 under 35 USC § 103(a) as allegedly being obvious over Scherzinger et al. in view of Sorge et al. and further in view of Tabor et al., and Dickinson (Journal of Cell Sciences (1983) 60: 355-365) is respectfully traversed.

The Examiner has merely restated the previous rejection. The combination of Scherzinger et al., Sorge et al., and Tabor et al. fail to disclose an amplification method without adding exogenous primers such that the amplified product is at least 10-fold greater than the amount of template DNA put into the mixture as the instant claims require. Dickinson fails to remedy the deficiencies of Scherzinger et al., Sorge et al., and Tabor et al., particularly because it fails to teach or suggest any amplification method wherein the amplification product is at least 10-fold grater than the input template DNA.

Applicants respectfully submit that this rejection should be withdrawn.

Claims 148 and 150

The rejection of claims 148 and 150 under 35 USC § 103(a) as allegedly being obvious over Scherzinger et al. in view of Sorge et al. and further in view of Tabor et al., and Peller et al. (Biochemistry (1977) 16(3): 387-395) is respectfully traversed.

The combination of Scherzinger et al., Sorge et al., and Tabor et al. fail to disclose an amplification method without adding exogenous primers such that the amplified product is at least 10-fold greater than the amount of template DNA put into the mixture.

Peller fails to remedy the deficiencies of Scherzinger et al., Sorge et al., and Tabor et al., because it fails to teach or suggest that the amplification product is at least 10-fold greater than the input template DNA.

Applicants respectfully submit that at least for this reason the instant claims are not obvious and this rejection should be withdrawn.

Claims 148, 151, and 152

The rejection of claims 148, 151, and 152 under 35 USC § 103(a) as allegedly being obvious over Scherzinger et al. in view of Sorge et al. and further in view of Tabor et al., and Nakai et al. (The Journal of Biological Chemistry (1993) 268(32): 23997-24004) is respectfully traversed.

For at least the reasons discussed above, the combination of Scherzinger et al., Sorge et al., and Tabor et al. fail to establish any *prima facie* case of obviousness with respect to the instant claims. Nakai fails to remedy the deficiencies of Scherzinger et al., Sorge et al., and Tabor et al., because it fails to teach or suggest that the amplification product is at least 10-fold greater than the input template DNA.

Accordingly, reconsideration and withdrawal of the section 103 rejection of claims 148, 151, and 152 are respectfully requested.

Claims 153, and 154

The rejection of claims 153 and 154 under 35 USC § 103(a) as allegedly being obvious over Scherzinger et al. in view of Sorge et al. and further in view of Tabor et al., and Engler et al. (The Journal of Biological Chemistry (1983) 258(18): 11197-11205) is respectfully traversed.

For at least the reasons discussed above, the combination of Scherzinger et al., Sorge et al., and Tabor et al. fail to establish any *prima facie* case of obviousness with respect to instant claims. Engler fails to remedy the deficiencies of Scherzinger et al., Sorge et al., and Tabor et al., particularly it fails to teach or suggest that the amplification product is at least 10-fold greater than the input template DNA.

Accordingly, reconsideration and withdrawal of the section 103 rejection of claims 153 and 154 are respectfully requested.

Claim 155

The rejection of claim 155 under 35 USC § 103(a) as allegedly being obvious over Scherzinger et al. in view of Sorge et al. and further in view of Tabor et al., and Jarvis et al. (The Journal of Biological Chemistry (1990) 265(25): 15160-15167) is respectfully traversed.

For at least the reasons discussed above, the combination of Scherzinger et al., Sorge et al., and Tabor et al. fail to establish any *prima facie* case of obviousness with respect to the instant claims. Jarvis fails to remedy the deficiencies of Scherzinger et al., Sorge et al., and Tabor et al., particularly it fails to teach or suggest that the amplification product is at least 10-fold greater than the input template DNA.

Accordingly, reconsideration and withdrawal of the section 103 rejection of claims 155 are respectfully requested.

Claims 161-164, and 169

The rejection of claims 161-164, and 169 under 35 USC § 103(a) as allegedly being obvious over Scherzinger et al. in view of Sorge et al. and further in view of Tabor et al., Bernstein et al., and Walker et al. is respectfully traversed.

The Examiner has just restated the previous rejection. The Examiner asserts that "[t]he combined teachings of Scherzinger, Sorge, and Bernstein result in the method of claims 24 and 160." Office Action mailed 12/11/07 at p. 23. As discussed previously and contrary to the Examiner's assertion, none of the prior art references provide any motivation to combine or provide any reasonable expectation of success to arrive at the invention of claims 24 (from which claims 161-164 depends) and 160, specifically a DNA isothermal amplification method generating an amplified product 100-1000,000 fold greater than input template DNA without the addition of exogenous primers or amplifying in an exponential manner.

The Examiner fails to address the arguments as they relate to the methods of Walker, presented in the previous response to Office Action, mailed 12/11/07. The Examiner's reliance on the teachings of Walker is misguided. As discussed previously, Walker's isothermal strand displacement amplification method is very different from that of Scherzinger, Sorge, Bernstein, and Tabor. Walker's method require the use of primer, and incubation with Hinc II and exo deficient Klenow polymerase (Walker et al. at p. 1691, right column, under "Introduction").

As described above, Walker et al. fails to cure the deficiencies of Scherzinger et al., Sorge et al, and Tabor et al, because the methods of Walker, like those of Sorge, require adding exogenous primers. As such, there would be no motivation to make the asserted combination as required to arrive at the instantly claimed method, and even if there was such motivation (although there is none), the combination of references still fail to provide any reasonable expectation of success to achieve the claimed method.

Accordingly, this rejection should be withdrawn.

CONCLUSION

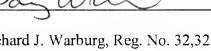
Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if any issue remains to be resolved in view of this communication so that a prompt disposition of the application can be achieved.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date 03/02/2009

By 

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